However, the Examiner states that Claims 7, 10, 14-31, 33-52 and 54-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b). Rule 1.142(b), however, is directed to claims which are to a nonelected invention, which is accurate for Claims 18-31, 33-52 and 54 but not for Claims 7, 10, 14-17 and 55-56. Moreover, the Examiner states that Claims 8-9, 11-13, 32 and 53 are objected to for being drawn to a non-elected invention. However, all of these claims are part of the elected invention of Group I. Applicants respectfully request clarification from the Examiner on the status of the claims. tri-peptide

Section 112, first paragraph, Rejections (Written Description)

The Examiner has rejected Claims 1-6, 9 and 11-13 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. For the reasons set forth below, this rejection is respectfully traversed.

The Examiner alleges that Claims 1-3 are drawn to mutant IMPDH of any structure and from any source, and that claims are also drawn to more than one isoform of the enzyme. The Examiner further alleges that the claim encompasses a genus of molecules described by the function of being an IMPDH enzyme, and that there is no limit to the structure of the oligopeptide and no limit to the region of the wild type IMPDH wherein the oligopeptide is substituted. Accordingly, the Examiner alleges that the specification of the present application fails to describe a representative number of species by any identifying characteristics other than the functionality of being an IMPDH.

The present invention is directed to modified IMPDH polypeptides having an oligo-peptide domain substituted for a subdomain of a wild-type IMPDH polypeptide, such that the substitution results in a modified IMPDH polypeptide which is shorter in length compared to the wild-type IMPDH polypeptide. As stated in the present specification, the modified molecules permit better resolution of the X-ray crystal structure of the modified IMPDH multimers complexed with an inhibitor. The substitute oligo-peptides have selected lengths and sequences which permit the folded modified IMPDH polypeptide to bind to inhibitors of IMPDH and/or retain the functional activity of wild-type IMPDH. Accordingly, the modified IMPDH polypeptides are useful for drug discover methods, such as structure-based design. (See, for example, page 5, lines 9-28 of present specification). Clear definitions of the inventive modified IMPDH polypeptides are provided, for example, at page 9, line 29 to page 10, line 11 of the present specification.

The Examiner states that Claims 1-3 are drawn to mutant IMPDH of any structure and from any source. However, Applicants respectfully point out that the claimed invention is directed to modified IMPDH polypeptides which are shorter in length than wild-type IMPDH, wherein a subdomain of the wild-type IMPDH is replaced with a shorter polypeptide, resulting in the modified

IMPDH. It is to this modification that the present invention is directed, the structure and source of the modified IMPDH is not relevant. The structure and source of the modified IMPDH may be anything that is within the scope of the claimed invention, namely any modified IMPDH having the requisite substituted region and which is useful for the purposes described in the specification. A representative structure of a modified IMPDH is provided, for example, in Figure 18.

The Examiner further states that the specification does not describe which amino acids of a wild-type IMPDH can be deleted, substituted, added or inserted and still impart the mutant protein with IMPDH activity. Applicants respectfully point out that the present specification clearly teaches that the portions of the wild-type IMPDH to be modified are the subdomain regions. These subdomain regions are readily identified by one skilled in the art, as discussed in the present specification at, for example, page 13, line 20 to page 14, line 28. One specific example is shown at page 49, lines 18-28, wherein a 133 amino acid residue subdomain region has been replaced with the tripeptide DKT, resulting in a modified IMPDH which is 384 amino acid residues in length, as compared to a 514 amino acid residue length of wild-type IMPDH. This modified IMPDH exhibits the functional activity of wild-type IMPDH (catalyzes NADH production) and binds to MPA. However, the modified IMPDH permits higher X-ray resolution as a result of its shorter length. Importantly, what is relevant is that substitution of the subdomain region results in a reduction of the overall length of the modified IMPDH polypeptide, permitting its use as discussed *supra* (see also, for example, page 14, lines 4-9 of the present specification).

Furthermore, working examples are provided which clearly illustrate possession of the claimed modified IMPDH polypeptides, including methods of making, characterizing and using them. Accordingly, Applicants respectfully disagree with the Examiner's position that the specification fails to describe representative species by any identifying characteristics other than the functionality of being an IMPDH. Rather, Applicants submit that the present specification clearly describes actual representative species which have been characterized as being useful for the purposes set forth in the present specification, namely better resolution of the X-ray crystal structure of the modified IMPDH multimers complexed with an inhibitor and, more generally, drug screening. Polynucleotide sequences are provided for several such representative species.

The Examiner alleges that Claims 4-5, 9 and 11-13 limit the invention to an array of tri-peptides, however, there is no limit to the region of the wild-type IMPDH where the oligopeptide is substituted. Applicants respectfully point out that Claims 4-5 are not directed to tri-peptides, although Claims 9 and 11-13 are directed to tri-peptides (Claims 9 and 11-13 each depend directly from Claim 6). With respect to Claims 9 and 11-13, Applicants submit that the same arguments provided *supra* are relevant to this rejection. The inclusion of tri-peptides in these claims merely illustrates a particular modification of the subdomain of a wild-type IMPDH, and numerous

examples of useful tri-peptides are provided in the present specification. See, for example, page 49, lines 18-28, previously discussed.

Applicants respectfully point out that Claim 6 stands rejected, but that the Examiner did not state the reason that Claim 6 is rejected. Furthermore, the Examiner states at the top of page 4 of the Office Action that applicants are not in possession of the "inventions of Claim 48, with dependent Claims 1-6, 9 and 11-13". However, Claim 48 is withdrawn from consideration as directed to a non-elected invention and, moreover, Claims 1-6, 9 and 11-13 do not depend from Claim 48.

For the reasons set forth above, Applicants respectfully submit that the present specification provides written description of the claimed modified IMPDH polypeptides. Withdrawal of the above rejections under Section 112, first paragraph, is appropriate and is respectfully requested.

Section 112, first paragraph, Rejections (Enablement)

The Examiner has rejected Claims 1-6, 9 and 11-13 under 35 U.S.C. §112, first paragraph, because the specification, while enabling for the mutant IMPDH of SEQ ID NO:30, does not provide enablement for a mutant IMPDH with an unlimited structure. The Examiner alleges that the specification does not enable any person skilled in the art to which it pertains, or with which it is most closely connected, to make the invention commensurate in scope with these claims. For the reasons set forth below, this rejection is respectfully traversed.

The Examiner again alleges that the claims are drawn to mutant IMPDH having unlimited structure and derived from any source. For the same reasons set forth above, Applicants submit that one skilled in the art can, using the teachings of the present specification, prepare modified IMPDH polypeptides for uses described in the specification and herein. The specification provides several working examples as to how modified IMPDH polypeptides of the present specification can be made and used, so it is unclear why the Examiner believes that one skilled in the art would not be able to make and use the claimed invention. The Examiner implies that undue experimentation would be needed to practice the claimed invention by citing *In re Wands*, but Applicants respectfully point out that no experimentation is needed. Rather, the specification clearly sets forth working examples, in addition to other teachings, which permit one skilled in the art to practice the claimed invention.

The Examiner alleges that the specification does not establish regions of the protein structure which may be modified without affecting IMPDH activity, although the specification clearly discusses that such regions are subdomains, and sets forth specific examples in which such a subdomain has been substituted (see, for example, page 49, lines 18-28, discussed *supra*). Commensurate with these teachings, one skilled in the art can modify subdomains of wild-type IMPDH polypeptides to prepare modified IMPDH polypeptides having the improved characteristics

disclosed in the specification and herein. Applicants respectfully submit that the present specification provides clear guidance necessary to make and use the claimed invention.

Therefore, withdrawal of the rejections under Section 112, first paragraph, is appropriate and is respectfully requested.

Section 112, second paragraph, Rejections (Definiteness)

The Examiner alleges that Claims 6-7 and 13-14 are indefinite for reciting "IMPDH", and that such recitation is not sufficient to convey with clarity that which applicant sees as his invention. Applicants assume that this rejection applies to Claims 1-6, 8-9, 11, 32 and 53 (although the Examiner does not clearly state that the rejection applies to claims other than Claims 6-7 and 13-14). Applicants respectfully point out that the use of abbreviations, such as in the present case, is appropriate where its meaning is clearly shown in the specification and also known in the art. In the present case, "IMPDH" stands for inosine-5'monophosphate dehydrogenase and is referenced by EC 1.1.1.205. Accordingly, Applicants submit that IMPDH is appropriately used in the pending claims.

Nonetheless, Applicants will amend the claims accordingly to spell out the full name of IMPDH in the first instance upon resolution of other issues in the present case.

Section 103 Rejection

The Examiner has rejected Claims 1-6, 11-13 and 32 under 35 U.S.C. §103(a) as being unpatentable over Zhang et al. ("Zhang") in view of Gibco BRL Products Catalog ("Gibco"). For the reasons set forth below, this rejection is respectfully traversed.

The Examiner alleges that Zhang teaches several bacterial/mammalian sequence signatures involved in subunit reactions, the active site flap and the NAD binding region. The Examiner further alleges that Zhang teaches that IMPDH is an attractive target for developing highly specific inhibitors, and that identification of catalytic regions refines the selection process and increases the probability that a signature sequence will be useful for the development of specific bacterial or mammalian IMPDH inhibitors. The Examiner acknowledges that Zhang fails to teach how to mutagenize IMPDH to arrive at a more refined signature region. However, the Examiner states that methods of mutagenesis are well known and practiced in the art, as shown by Gibco.

Applicants have read Zhang and point out that Zhang discloses the use of IMPDH as a target for possible antimicrobial agents, and discusses the desirability of determining IMPDH regions which are useful for targeting. This is consistent with the discussion in the Background section of the present application, which states that efforts to identify agents that selectively inhibit the catalytic activity of IMPDH are known. However, the present invention is directed to novel

polypeptides which have a modified wild-type IMPDH sequence (wherein the subdomain region of the wild-type has been replaced). This results in a modified IMPDH polypeptide which is shorter in length than a wild-type IMPDH polypeptide and, accordingly, is better suited for X-ray crystal structure analysis. None of this is either taught or suggested by Zhang. Gibco, which merely sets forth known mutagenesis techniques, fails to remedy the clear deficiencies of Zhang.

For the reasons set forth above, Applicants respectfully submit that withdrawal of the rejections under Section 103 is appropriate and is respectfully requested.

Please direct any questions concerning this Response or any aspect of this case to the undersigned attorney.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Account No. 19-3880 in the name of Bristol-Myers Squibb Company.

Respectfully submitted,

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